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TITLE: A Phase II Study of Merestinib in Non-Small Cell Lung Cancers Harboring *MET* Exon 14 Mutations and solid tumors with *NTRK* rearrangements

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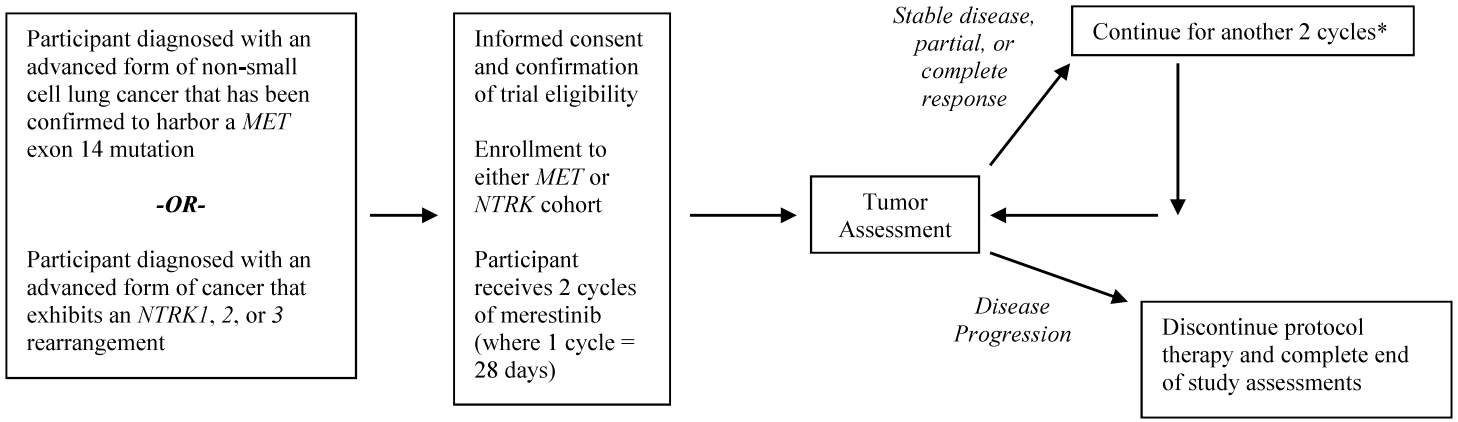
SCHEMA



*In the absence of treatment delays due to adverse events, treatment may continue until disease progression (unless the patient is exhibiting clinical benefit as agreed upon by the principal investigator), intercurrent illness that prevents further treatment, pregnancy, a change in the patient's condition rendering the patient unacceptable for further treatment in the judgment of the investigator, or the participant decides to withdraw from the study.

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1. OBJECTIVES

1.1 Study Design

This is an open-label, phase II study of merestinib in patients with advanced non-small cell lung cancer (NSCLC) with a *MET* exon 14 mutation or patients with advanced cancer harboring an *NTRK1, 2,* or *3* rearrangement. Patients with a *MET* mutation will be evaluated in a single-arm design. A small cohort of *NTRK* patients will be evaluated for exploratory purposes.

1.2 Primary Objective

- Examine the overall response rate (ORR) utilizing RECIST 1.1 criteria in patients harboring *MET* mutations following administration of merestinib.

1.3 Secondary Objectives

- Evaluate the safety and tolerability of merestinib.
- Determine the overall survival (OS) rate, defined as the time from registration to death due to any cause (or censored at date last known alive), in patients harboring *MET* mutations.
- Determine the progression-free survival (PFS) rate in patients harboring *MET* mutations, defined as the time from registration to disease progression or death due to any cause. Participants alive without disease progression will be censored at date of last disease evaluation.
- Determine the duration of response (DoR) in patients harboring *MET* mutations, defined as the time from documentation of response (by RECIST 1.1 criteria) to disease progression, or censored at date of last disease evaluation for those without progression.

1.4 Exploratory Objectives

- Explore the ORR, OS, PFS, and DoR in a small cohort of patients with advanced cancer harboring an *NTRK1, 2,* or *3* rearrangement.
- Investigate the genomic determinants of response and resistance to merestinib by analyzing circulating free tumor DNA for identification of activating mutations/rearrangements in *MET* or *NTRK* as well as for detection of resistance mutations.
- Examine the mechanisms of resistance to prior tyrosine kinase inhibitors (TKIs) via a pre-treatment biopsy obtained on patients enrolling to the trial who have received a prior *MET* or *NTRK* inhibitor.
- Assess the genomic determinants of response and resistance to merestinib by analyzing tumor tissue obtained from patients at the time of disease progression.

2. BACKGROUND

2.1 Study Diseases

Lung cancer remains the third most prevalent cancer in the United States and more people die of lung cancer than any other form of cancer[1]. The application of molecularly targeted therapies in subsets of lung cancer patients has revolutionized treatment for patients whose tumors harbor

mutations in genes such as *EGFR, ALK,* and *ROS1*. Activating mutations and genomic amplifications in the mesenchymal-to-epithelial transition (*MET*) gene have also been described as a potentially important therapeutic target in NSCLC[2-4]. Somatic mutations in the *MET* gene can lead to exon 14 skipping, and this mutant receptor can then subsequently increase c-Met signaling and oncogenic potential[5,6].

MET exon 14 mutations have been identified in approximately 3% of non-squamous NSCLCs. The mutation seems to occur primarily in older adults, a group that may not be able to receive full-dose chemotherapy due to comorbidities. Successful identification of targetable mutations may improve tolerability and ultimately treatment outcome in these patients[7].

Neurotrophic tyrosine receptor kinases (NTRK) belong to a group of tyrosine kinases that usually help regulate neural development. Chromosomal rearrangements that result in the expression of oncogenic *NTRK* fusions can induce cancer cell proliferation and engage critical cancer-related downstream signaling pathways. These rearrangements have been identified to occur in a subset of epithelial malignancies and can provide the basis for sensitivity to kinase inhibitors[8,9]. *NTRK* rearrangements are rare and are found among a diverse group of cancers, including thyroid and secretory breast carcinomas, NSCLC, sarcomas, and other epithelial malignancies[10].

2.2 Merestinib (LY2801653)

Merestinib is a potent and selective type II *MET/RON* kinase inhibitor with the ability to achieve inhibition of *MET* activity both *in vitro* and *in vivo*. Merestinib has also been shown to be capable of inhibiting 14 receptor tyrosine kinases, including *MET*, *MST1R* [*RON*], *AXL*, *ROS1*, *PDGFRA*, *FLT3*, *MERTK*, *TYR03*, *TEK*, *DDR1*, *DDR2*, and *NTRK1/2/3*, as well as two serine/threonine kinases (*MKNK1/2*) [11]. Given that *MET* and other targets of merestinib may play critical roles in cancer progression, inhibition of *MET* and other targets by merestinib could have a significant impact on the treatment and survival of cancer patients[12-17].

The first-in-human phase I study for merestinib (Study I3OMC-JSBA, hereby referred to as JSBA) was initiated in September 2009 and is currently ongoing. The objectives of this study were to evaluate the safety and tolerability of merestinib in patients with cancer and to determine the dose and schedule for phase II studies. As of 20 August 2015, 166 patients with advanced cancer have been enrolled and have received merestinib at dose levels ranging from 3 mg per day to 240 mg per day.

Study JSBA consists of six parts (A through F):

A. single agent dose-escalation testing in patients with advanced or metastatic solid tumors,
B. single agent dose-confirmation testing,
C. dose finding in combination with cetuximab,
D. dose finding in combination with cisplatin,
E. safety testing in combination with gemcitabine and cisplatin, and
F. safety testing in combination with ramucirumab

Enrollment has been completed for parts A-E. Based on the interim analysis of data from the

dose escalation, the 120 mg dose was investigated in part B of the study with merestinib as a single agent in patients with adenocarcinoma of the colon or rectum, squamous cell carcinoma of the head and neck (HNSCC), cholangiocarcinoma, and metastatic uveal melanoma. Additional parts of the study have enrolled patients to evaluate the safety of merestinib when administered in combination with other standard regimens.

A clinical pharmacology study with merestinib (Study I3O-EW-JSBC, or JSBC) was initiated in November 2013 to determine the routes of elimination and extent of metabolism of merestinib, including identification of metabolites in plasma, urine, and feces in sterile healthy subjects after a single oral administration of merestinib containing ^{14}C- merestinib. The total administered dose of merestinib was 120 mg. A total of five healthy subjects received merestinib containing ^{14}C-merestinib in this study. This study was completed on 18 September 2014.

Another clinical pharmacology study with merestinib (Study I3O-EW-JSBD, or JSBD) was initiated in February 2015 to determine the relative bioavailability of two tablet formulations of merestinib, and the effect of a high-fat meal on the bioavailability of merestinib administered as three 40 mg tablets of the test formulation. A total of 23 subjects received merestinib. This study was completed on 06 October 2015.

2.2.1 Merestinib Pre-Clinical Studies

The plasma toxicokinetics of merestinib and its active *N*-desmethyl metabolite LSN2800870 were evaluated in Sprague-dawley rats and Beagle dogs following daily oral administration of merestinib for 4 weeks. In rats, exposure to merestinib (defined as maximal concentration [C_{max}] and area under the concentration-time curve from time 0 to 24 hours [$AUC_{0\text{-}24\ hr}$]) generally increased more than proportionally from 3 to 30 mg/kg/day. Exposure to merestinib in male rats trended slightly lower than in females (< 2-fold). No accumulation was observed after multiple doses. Merestinib was converted to an active metabolite, LSN2800870, with higher concentrations in male rats than female rats.

In dogs, merestinib C_{max} and $AUC_{0\text{-}24\ hr}$ increased less than dose proportionally from 2 to 250 mg/kg/day. Potential accumulation of merestinib and LSN2800870 in dog plasma was observed following multiple dosing of merestinib at the 2 and 25 mg/kg dose levels. Gender differences in exposure were not marked (< 2-fold). Merestinib was not extensively converted to LSN2800870 in dogs.

Absorption, distribution, metabolism, and excretion of merestinib in rats and dogs have been determined following single doses of ^{14}C- merestinib. Parent merestinib is absorbed and is the main component circulating in the plasma of both species. The *N*-desmethyl metabolite, LSN2800870, was observed in plasma, representing an approximately 9-fold lower exposure in rats and 27-fold lower in dogs when compared with the parent. More metabolites were observed in rat feces, bile, and plasma than in dog feces and plasma. Metabolic transformations observed in formation of the metabolites included oxidation, glucuronide conjugation, and *N*-desmethylation. The radioactivity associated with ^{14}C- merestinib was extensively distributed in tissues and organs and selectively associated with melanin-containing tissues in rats. The major path of excretion in rats and dogs was biliary/fecal based on the recovery of total radioactivity.

Less than 3% of the dose was excreted in the urine.

Pre-clinical Pharmaco- and Toxicokinetics

The pharmacokinetic (PK) parameters of merestinib and merestinib-derived radioactivity were evaluated in male Sprague-dawley rats and male Beagle dogs following a single oral dose. On the basis of AUC versus time curve values, with time from 0 to infinity ($AUC_{0-\infty}$), merestinib accounted for 64.9% and 83% of the plasma radioactivity in rats and dogs, respectively. The elimination half-life ($t_{1/2}$) of merestinib was similar to the elimination $t_{1/2}$ of radioactivity.

Table 1: Mean (± SD) Plasma Pharmacokinetic Parameters following a Single 10 mg/kg Oral Dose of ^{14}C-merestinib in Sprague-dawley rats and Beagle dogs (n=3)

Parameter	Rat	Dog	Rat	Dog
	Merestinib		Radioactivity	
C_{max} (ng/mL or ng-eq/mL)	1810 ± 720	7510 ± 1390	2650 ± 890	10,300 ± 2400
T_{max} (hour)	4	3 ± 1	4	3 ± 1
Half-life (hour)	4.24	17.3 ± 1.1	6.26	14.9 ± 3.6
$AUC_{0-\infty}$ (ng·hr/mL or ng-eq·hr/mL)	19,400	200,000 ± 73,000	29,900	241,000 ± 91,000

Abbreviations: $AUC_{0-\infty}$ = area under the plasma concentration versus time curve from time 0 extrapolated to infinity; C_{max} = maximum observed plasma concentration; SD = standard deviation; T_{max} = time to C_{max}.

Due to the lower than expected exposure from the free-base dry blend capsule used in the 3 and 6 mg cohorts in Study JSBA, a formulation study was conducted in dogs to evaluate the plasma exposure of 5 alternative formulations and a tosylate salt compared with the free-base dry blend capsule at 6 mg/kg. The 5 alternative formulations were standard wet granulation with surfactant, polyvinylpyrrolidone vinylacetate (PVP-VA) solid dispersion with surfactant, HPMCAS solid dispersion with surfactant, PEG 3350 (polyethylene glycol)/10% Gelucire® 44/14 (9:1) semisolid, and γ-cyclodextrin with wet granulation. All formulations and the salt increased plasma exposure compared with the FHD capsule. The exposure increase was the highest for HPMC-AS solid dispersion with an $AUC_{0-24\ hr}$ increase of 30-fold followed by the semi-solid with a 20-fold increase. The PVP-VA solid dispersion led to a 13-fold increase and the tosylate salt to an 8.2-fold increase. The standard wet granulation with surfactant provided a 2.8-fold increase, and γ-cyclodextrins provided the smallest difference with only a 2.1-fold increase compared with the dry blend.

A study was conducted in Pgp and Bcrp knockout mice to determine the role of Pgp/Bcrp transporters on the PK of merestinib following 0.1, 1, and 10 mg/kg oral administration. The $AUC_{0-24\ hr}$ in the individual Pgp (Mdr 1a/b) and Bcrp knockout mice was increased less than 2-fold when compared with wild-type FVB mice. However, exposure increased 2.3-fold in Mdr1a/b/Bcrp triple-knockout mice. These data indicate that transporters, including Pgp and Bcrp, appear to be involved in the absorption and/or clearance of merestinib in mice.

The plasma toxicokinetics of merestinib and its active *N*-desmethyl metabolite, LSN2800870,

were evaluated on study days 1 and 28 following oral administration of 3, 10, or 30 mg/kg/day to rats for 4 weeks and is summarized in Table 2.

In the rat, exposure to merestinib and its metabolite LSN2800870 (defined as C_{max} and $AUC_{0\text{-}24\ hr}$) generally increased more than proportionally from 3 to 30 mg/kg/day. All animals in the high-dose group were euthanized prior to the study end and not available for blood draws on Day 28. In this study, merestinib was orally available, with time to maximal plasma concentration (t_{max}) ranging from 2 to 8 hours for the parent and 4 to 12 hours for the metabolite. The exposure to merestinib in male rats was slightly lower than the exposure in females, but the difference was < 2-fold. The values for merestinib C_{max} and $AUC_{0\text{-}24\ hr}$ on day 28 were slightly lower than those on day 1, but there was no evidence of total CYP induction after multiple dosing, nor was the metabolite exposure increased. The C_{max} and $AUC_{0\text{-}24\ hr}$ values for the metabolite were markedly (> 2-fold) higher in males than in females.

Table 2: Mean Toxicokinetic Parameters in Sprague-dawley Rats after Single and Multiple Oral Dose Administration of Merestinib for 4 Weeks

Parameter	Merestinib Administered Dose (mg/kg)					
	3		10		30	
Sex[a]	M	F	M	F	M	F
Merestinib						
Day 1:						
C_{max} (ng/mL)	641	855	3353	3200	8160	10,800
$AUC_{0\text{-}24\ hr}$ (ng·hr/mL)	8082	12,606	34,209	39,733	125,233	166,963
Day 28:						
C_{max} (ng/mL)	404	784	2153	2540	NA	NA
$AUC_{0\text{-}24\ hr}$ (ng·hr/mL)	4903	7563	20,934	31,110	NA	NA
LSN2800870						
Day 1:						
C_{max} (ng/mL)	56.8	14.6	321	106	835	314
$AUC_{0\text{-}24\ hr}$ (ng·hr/mL)	728	249	4047	1218	13,508	5104
M/P ratio $AUC_{0\text{-}24\ hr}$	0.0901	0.0198	0.118	0.0307	0.108	0.0306
Day 28:						
C_{max} (ng/mL)	31.7	13.8	262	81.6	NA	NA
$AUC_{0\text{-}24\ hr}$ (ng·hr/mL)	541	148	2677	932	NA	NA
M/P ratio $AUC_{0\text{-}24\ hr}$	0.110	0.0196	0.128	0.0300	NA	NA

Abbreviations: $AUC_{0\text{-}24\ hr}$ = area under the plasma concentration versus time curve from time zero to 24 hours; C_{max} = maximum observed plasma concentration; F = female; M = male; M/P Ratio $AUC_{0\text{-}24\ hr}$ = metabolite/parent ratio calculated using $AUC_{0\text{-}24\ hr}$ and not adjusted for the molecule weight of parent and metabolite; NA = not applicable.

[a] N=3 rats/sex/time point.

In Beagle dogs, the plasma toxicokinetics of merestinib and its *N*-desmethyl metabolite LSN2800870 were evaluated on study day 1 and again on either day 15 or day 28 following oral administrations of 2, 25, or 250/125 mg/kg/day to dogs for 4 weeks. Toxicokinetic parameters

are summarized in Table 3.

Following oral administration, merestinib was available with mean t_{max} values ranging from 1.2 to 12.7 hours. Exposure increased less than dose proportionally from 2 to 250 mg/kg/day. Variability of $AUC_{0\text{-}24\ hr}$ for the parent, as expressed by the percentage coefficient of variation (%CV), ranged from 6% to 60%. No marked gender difference (< 2-fold) on exposure was observed. Accumulation occurred following multiple dosing. Exposure of dogs to the metabolite was low.

Table 3: Mean Toxicokinetic Parameters in Beagle Dogs after Single and Multiple Oral Dose Administrations of Merestinib for 4 Weeks

Parameter	Merestinib Administered Dose					
Dose (mg/kg)	2		25		250/125[a]	
Sex	M	F	M	F	M	F
Merestinib						
Day 1						
C_{max} (ng/mL)	175	89.7	1419	882	6050	4760
$AUC_{0\text{-}24\ hr}$ (ng·hr/mL)	2505	1570	22,158	15,430	104,052	84,776
Day 15						
C_{max} (ng/mL)	NA	NA	NA	NA	3615	2783
$AUC_{0\text{-}24\ hr}$ (ng·hr/mL)	NA	NA	NA	NA	51775	39228
Day 28						
C_{max} (ng/mL)	254	208	2000	1280	NA	NA
$AUC_{0\text{-}24\ hr}$ (ng·hr/mL)	3659	3291	26,708	19,856	NA	NA
LSN2800870						
Day 1						
C_{max} (ng/mL)	2.99	1.85	32.4	23.0	168	140
$AUC_{0\text{-}24\ hr}$ (ng·hr/mL)	44.1	35.3	577	414	3126	2548
M/P ratio $AUC_{0\text{-}24\ hr}$	0.0176	0.0224	0.0271	0.0270	0.0316	0.0290
Day 15						
C_{max} (ng/mL)	NA	NA	NA	NA	80.0	57.9
$AUC_{0\text{-}24\ hr}$ (ng·hr/mL)	NA	NA	NA	NA	1325	1001
M/P ratio $AUC_{0\text{-}24\ hr}$	NA	NA	NA	NA	0.0250	0.0245
Day 28						
C_{max} (ng/mL)	5.60	4.56	58.4	36.9	NA	NA
$AUC_{0\text{-}24\ hr}$ (ng·hr/mL)	89.1	80.9	849	631	NA	NA
M/P ratio $AUC_{0\text{-}24\ hr}$	0.0236	0.0247	0.0329	0.0323	NA	NA

Abbreviations: $AUC_{0\text{-}24\ hr}$ = area under the plasma concentration versus time curve from time zero to 24 hours; C_{max} = maximum observed plasma concentration; F = female; M = male; M/P ratio $AUC_{0\text{-}24hr}$ = metabolite/parent ratio calculated using $AUC_{0\text{-}24\ hr}$ and not adjusted for the molecule weight of parent and metabolite; NA = not applicable.

[a] High-dose group animals were dosed at 250 mg merestinib/kg on Days 1 through 5. Following a dosing holiday, and beginning on Day 15, animals were dosed at 125 mg merestinib/kg but were sacrificed at Day 21.

Note: N=3 to 5 animals per group.

Distribution

In preliminary studies, merestinib was administered via gavage at 50 mg/kg to nude mice bearing S114 tumors (derived from ovary cells). Merestinib was distributed into tumors with a tumor-to-plasma ratio of 0.55 in mice at 2 hours post-dose.

A quantitative whole-body autoradiographic disposition study was conducted in male and female

pigmented Long Evans rats and male non-pigmented Sprague-dawley rats following a single 10 mg/kg oral dose of ^{14}C-merestinib. Radioactivity related to ^{14}C-merestinib was extensively distributed into tissues and was selectively associated with melanin-containing tissues. Maximum concentrations of radioactivity for Long Evans rats were observed at 4 hours post-dose, and concentrations generally declined over time. The liver, uveal tract of the eye, epididymis (male), pigmented skin, small intestine, and thymus (female) were the tissues with the highest concentrations. Very low levels of radioactivity crossed the blood-brain barrier and blood-testis barrier.

Metabolism

The metabolism of merestinib was studied *in vitro* in rat, dog, and human cryopreserved hepatocytes, and *in vivo* in rats and dogs. The parent compound undergoes oxidative metabolism producing 2 predominant metabolites: LSN2800870 (*N*-desmethylation) and LSN2887652 (oxidation of methylpyridone). LSN2800870 and LSN2887652 are both active metabolites.

The metabolism of merestinib was examined in intact or biliary cannulated male Sprague-dawley rats following a single 10 mg/kg oral dose of ^{14}C-merestinib, and male Beagle dogs following a single 1 mg/kg intravenous or 10 mg/kg oral dose of ^{14}C- merestinib. More metabolites were observed in rat feces, bile, and plasma (a total of 22) than in dog feces and plasma (total of 9). Urine was not profiled due to the low renal excretion of total radioactivity. The primary metabolic pathways observed in rats involved *N*-desmethylation of the *N*-methylindazole followed by oxidation and/or glucuronide conjugation on either the indazole or pyrazole moiety, and oxidation of the methyl substituent on the methylpyridone. An additional pathway that involved direct N-linked glucuronide conjugation was observed in dogs.

Excretion

Excretion studies using ^{14}C- merestinib were conducted following administration of a single oral or intravenous dose to rats and dogs. The majority of the dose was excreted in the bile or feces. Renal excretion was negligible.

Pre-Clinical Safety

Merestinib was evaluated in one month daily oral dosing studies in rats and dogs (with 1 month reversibility) at dose levels predicted to be biologically efficacious in humans, as well as at doses well in excess of those predicted to be biologically efficacious. In addition, a standard battery of safety pharmacology, genetic toxicity, and embryo-fetal development studies were performed.

Daily administration of merestinib in rats caused non-formed feces at a tolerated dose level, which became more severe (liquid feces) at dose levels that exceeded the maximum tolerated dose (MTD). Target organ toxicity was observed at both tolerated and non-tolerated dose levels in both species. Target organ toxicities at tolerated dose levels included renal glomerulopathy, characterized by expansion of the renal glomerular mesangium. This change was observed in rats at all dose levels (primarily minimal to slight at the low dose, with increasing severity with increasing doses), accompanied by minimal to slight proteinaceous tubular casts mainly at the

high dose. This change was not reversible. Although there were no adverse functional effects (based on clinical chemistry), this change might be predicted to lead to adverse effects on glomerular function over time. However, similar effects were not observed in dogs. These changes may be related to the anti-angiogenic effects of merestinib.

Additional target organ toxicities observed at tolerated dose levels included lymphoid organ necrosis, ovarian granulosa cell necrosis, bone physeal effects, bone marrow hypercellularity and increased myeloid-erythroid ratio, and testicular degeneration. Additional target organ toxicities observed at dose levels that exceeded the MTD included: adrenal gland congestion/hemorrhage; bone metaphyseal necrosis; myocardial degeneration/inflammation; vascular degeneration in the heart, gastrointestinal system, and pancreas; and male mammary gland necrosis. Merestinib also causes complete post-implantation loss at higher dose levels in rats exposed during the period of organogenesis.

Most of the toxicity observed in non-clinical species was reversible and is clinically monitorable: tremors, inflammatory leukogram, soft feces, lymphoid organ injury, adrenal gland injury, liver injury, and heart functional effects. The renal glomerular changes were not reversible; however, they did not have adverse functional consequences. The bone effects may be relevant only in growing bone (e.g., in children). Heart, vascular, and male mammary gland effects were only observed in a single species at dose levels well in excess of the MTD. Ovarian/testicular injury is a common toxicity observed with anti-cancer treatments.

Pre-clinical Pharmacology

The hepatocyte growth factor (HGF)/*MET* signaling pathway regulates a wide variety of normal cellular functions that can be subverted to support neoplasia including cell proliferation, survival, apoptosis, scattering and motility, invasion, and angiogenesis. For these reasons, merestinib was developed through a strategy of targeting the *MET* receptor. Additional biochemical and cell-based assay testing have demonstrated that merestinib is a type II adenosine triphosphate competitive inhibitor of 14 receptor tyrosine kinases (*MET*, *MST1R* [also known as *RON*], *AXL, ROS1, PDGFRA, FLT3, MERTK, TYR03, TEK* [also known as *TIE2*], *DDR1, DDR2, NTRK1, NTRK2,* and *NTRK3*) and two serine/threonine kinases (*MKNK1/2*). The two main circulating metabolites of merestinib (LSN2800870 and LSN2887652) found in both non-clinical studies in rats and dogs and the clinical Study JSBC were found to have similar kinase inhibitory activity as the parental compound in all the above targets when screened *in vitro* against a 456-kinase panel (DiscoveRx scanMax™).

Merestinib inhibits autophosphorylation of the human *MET* receptor with a concentration producing 50% inhibition (IC_{50}) of 0.2 μM and an inhibition binding constant (K_i) of 0.002 μM. It is a compound with a slow off-rate and a $t_{1/2}$ of 525 minutes *in vitro* in a dissociation assay. Merestinib inhibits phosphorylation of *MET* in HGF-stimulated H460 lung cancer cells with IC_{50} of 0.035 μM. It also inhibits *MET* phosphorylation in an autocrine cell line S114 with IC_{50} of 0.059 μM. Merestinib is active against 13 mutant forms of *MET* (Y1248C, D1246N, V1110I, M1268T, V1206L, L1213V, K1262R, M1149T, V1238I, S1058P, H1124D, G1137V, and H1112Y) with similar potency[11]. With the exception of S1058P, which is a mutation in the juxtamembrane domain, the remaining 12 mutations are in the *MET* kinase domain.

Merestinib demonstrates anti-angiogenic activity *in vitro* in human umbilical vein endothelial cell (HUVEC) migration assays and endothelial cell cord formation assays.

Merestinib demonstrates phospho-*MET* (p-*MET*) inhibition in nude mice bearing S114 xenograft tumors with a threshold effective dose of 50% inhibition (TED_{50}) of 1.24 mg/kg, and a TED_{90} (threshold effective dose of 90% inhibition) of 7.4 mg/kg. Sustained target inhibition (94% p-*MET* inhibition) was observed at 8 hours after a single 120 mg/kg dose (TED_{95} [threshold effective dose of 95% inhibition]).

When dosed as a single agent, merestinib has demonstrated inhibition of tumor proliferation in U87MG glioblastoma, NSCLC (H441, A549, H1299, EBC-1), colon cancer (HT-29, HCT-116, KM-12, EL-1989), renal cell carcinoma (Caki-1, 786-0), MV4-11 acute myeloid leukemia, KP4 pancreatic cancer, cholangiocarcinoma (EGI-1, SNU-869, SNU-1196, CTG-0011, CTG-0399), pediatric cancer (SJCRH30, RD-ES), and MKN45 gastric cancer xenograft tumor models following oral administration with either a daily or intermittent dosing regimen (9 days on, 5 days off or 5 days on, 2 days off). Merestinib treatment also demonstrates anti-tumor activity in both the H441 and H1299 non-small cell lung orthotopic mouse models[18]. When studied in the H441 orthotopic model, merestinib reduced primary tumor growth and lymph node metastasis and was associated with a prolongation of survival in tumor-bearing animals.

In addition to cell line-derived xenograft and orthotopic tumor models, merestinib demonstrated anti-tumor efficacy in human primary tumor-derived xenograft models of lung, pancreas, liver, breast, colorectal, cholangiocarcinoma (CCA), and kidney. Both KM-12 and EL-1989 bear the *TPM3-NTRK1* fusion as a result of chromosomal translocation. In both cell line-derived and human primary tumor-derived animal models, merestinib demonstrated anti-tumor activity in tumors bearing both wild-type and activating mutations of *KRAS*. In *MET*-dependent xenograft models (autocrine *MET* activation or *MET* over expression), merestinib displayed anti-proliferation effects on tumor cells and anti-angiogenesis effects on tumor vasculature. Combination treatment of merestinib with anti-vascular endothelial growth factor receptor 2 (VEGFR2) antibody DC101 (a surrogate of ramucirumab) in xenograft models for gastric cancer (MKN45), pediatric cancer (SJCRH30, A204, Y79, RD-ES), and CCA (EGI-1, SNU-1196) resulted in further anti-tumor effect.

Enzyme Inhibition

The potential for drug-drug interactions (DDIs) was evaluated *in vitro* in human microsomes where merestinib exhibited a potential for competitive inhibition of CYP2C19, CYP2C9, and CYP2C8 yielding an apparent K_i of 0.97, 0.65, and 0.29 μM, respectively. The K_i for CYP3A4, CYP2D6, CYP2B6, and CYP1A2 were not calculated due to < 50% inhibition at the highest concentration tested (3 μM) in the assay. Merestinib was not tested at higher concentrations due to insolubility in the system at concentrations >3 μM. Since a steady-state C_{max} in the range of 502 ng/mL (0.9 μM) merestinib was observed in Study JSBA, there may be a potential for DDIs when merestinib is co-administered at doses of 80 mg or higher with substrates of CYP2C19, CYP2C8, and CYP2C9.

While initial screening data with merestinib suggested possible mechanism-based inhibition of CYP3A4 (testosterone) and CYP2C9 at a concentration of 3 μM, a more rigorous assessment of mechanism-based inhibition of CYP3A in the concentration range of 0.375 to 12 μM indicated that merestinib is not a time-dependent inhibitor of CYP3A. No mechanism-based inhibition was observed with CYP2D6, CYP2C19, CYP2C8, CYP2B6, or CYP1A2.

Enzyme Induction

The ability of merestinib to induce catalytic activities associated with CYP1A2, CYP2B6, and CYP3A was examined in primary cultures of fresh human hepatocytes. The results indicated that merestinib is unlikely to cause clinically relevant *in vivo* induction of CYP1A2, CYP2B6, or CYP3A within the concentration range examined (0.005 to 5 μM).

Clearance

A substrate depletion approach employing human recombinant CYPs indicated that CYP3A is responsible for 99% of hepatic clearance, and CYP1A2, CYP2B6, and CYP2J2 are each responsible for < 1% of hepatic CYP-mediated clearance of merestinib. The contributions of other non-CYP elimination pathways were not measured in this assay and must be accounted for when estimating total clearance and/or the potential for a co-administered drug to affect the clearance of merestinib.

2.2.2 Merestinib Clinical Studies

As of 20 August 2015, a total of 166 patients in Study JSBA were treated with at least one dose of study drug. Merestinib has also been administered in a total of 28 healthy subjects (Studies JSBC and JSBD).

Human Pharmacokinetics

Merestinib PK has been investigated with drug-in-capsule or enabled formulation at dose levels from 3 to 6 mg and from 5 to 240 mg, respectively. Pharmacokinetic interactions with concomitant drugs have not yet been assessed with merestinib. Data in patients from the first two cohorts in Study JSBA, who were dosed with the capsule formulation, indicated limited absorption. To increase the bioavailability of drug, an enabled dosage form was introduced. Data from patients who received this formulation indicated that a significant increase in exposure was achieved compared to previous cohorts receiving the drug-in-capsule formulation.

In a non-compartmental analysis comprising concentration data from 113 patients in Study JSBA through June 2015, observed C_{max} and $AUC_{0\text{-}24\ hr}$ indicate that exposure increases with dose of the enabled formulation following single doses from 5 to 240 mg. The geometric mean of the oral apparent volume of distribution during the terminal phase (V_z/F) was 287 L (53% CV), and the apparent oral clearance (CL/F) was 19.3 L/h (36% CV), leading to a typical $t_{1/2}$ of 10.3 hours (42% CV). Given the range of t_{max}, there is extensive variability in the rate of absorption and, in patients with cancer; variability in absorption and bioavailability contributes to the variability in

exposure. The mechanisms and covariates that may explain this variability (e.g., metabolism) remain under investigation.

Table 4: Merestinib Non-compartmental PK Parameters Following First Dose, Study JSBA

Dose	5 mg	10 mg	20 mg	40 mg	80 mg	120 mg	160 mg	240 mg
N	3	4	4	3	42	42	12	3
C_{max}	10.1	22.7	56.8	85.7	264	410	374	828
(ng/mL)	(90)	(122)	(47)	(17)	(58)	(49)	(69)	(15)
t_{max}[a]	5	3.03	3	5.08	5	4.45	5.03	5
(h)	(2 – 5.25)	(2 – 6)	(2 – 26)	(5.02 – 26)	(2.05 – 26.43)	(2 – 24)	(2.02 – 26)	(4.47 – 5)
AUC(0-∞)	216	543	1150[b]	1810[b]	4300[g]	6270[c]	7550[d]	11400
(ng•h/mL)	(73)	(47)	(41)	(16)	(41)	(34)	(25)	(14)
AUC(0-t_{last})	90.6	332	473	1340	3000	4530	4600	9690
(ng•h/mL)	(328)	(89)	(134)	(6)	(60)	(50)	(59)	(8)
AUC(0-24)	142	316	720[e]	1260	3070[h]	4580[h]	4360	9430
(ng•h/mL)	(80)	(92)	(37)	(4)	(45)	(47)	(64)	(9)
CL/F	23.2	18.4	17.4[b]	22.1[b]	18.6[g]	19.1[c]	21.2[d]	21.1
(L/h)	(73)	(47)	(41)	(16)	(41)	(34)	(25)	(14)
V_z/F	457	433	313[b]	390[b]	269[g]	270[c]	327[d]	239
(L)	(96)	(116)	(32)	(4)	(53)	(47)	(49)	(26)
$t_{1/2}$	13.7	16.3	12.5[b]	12.2[b]	10[g]	9.79[c]	10.7[d]	7.85
(h)	(23)	(55)	(8)	(12)	(46)	(37)	(50)	(40)

Abbreviations: %CV = % coefficient of variation; $AUC_{0-\infty}$ = area under the concentration–time curve from time zero to infinity after the first dose; AUC_{0-24} = area under the concentration time curve from 0 to 24 hours after the first dose; $AUC_{0-tlast}$ = area under the concentration time curve from time zero the last measurable or sampled concentration after the first dose; CL/F = apparent total body clearance of drug calculated after oral administration; C_{max} = maximum concentration observed after first dose; Max = maximum; Min = minimum; PK = pharmacokinetic; $t_{1/2}$ = half-life; t_{max} = time when C_{max} was observed; V_z/F= apparent volume of distribution during the terminal phase.

Note: Values Are Reported as Geometric Mean (%CV) unless otherwise noted.

[a] Median (Min - Max).
[b] N=2
[c] N=38
[d] N=10
[e] N=3
[f] N=28
[g] N=34
[h] N=40

Study JSBD was designed to investigate the relative bioavailability of a test formulation compared to the reference formulation, as well as to investigate the effect of a high-fat meal on the bioavailability of merestinib, administered as the test formulation. The PK analysis was carried out with data from 23 individuals, and a comparison of fasted versus fed state (US Food and Drug Administration-defined high-fat meal) indicated a significant increase in bioavailability of merestinib with concomitant food intake.

Following administration of 120 mg merestinib in the fed state, geometric least squares mean merestinib AUC from time zero to the last measurable concentration after the first dose ($AUC_{0-tlast}$), $AUC_{0-\infty}$, and C_{max} were, respectively, 2.29, 2.28, and 2.44 times that following administration of 120 mg merestinib in the fasted state, and these differences were statistically significant. The median t_{max} of merestinib occurred 2 hours later in the fed states compared to the

fasted state. A similar increase in exposure was observed for the major metabolites. However, the mean merestinib exposures observed in the fasted state in Study JSBD was marginally lower compared to those observed at the same 120 mg dose level in Study JSBA ($AUC_{0-\infty}$ 4930 ng•h/mL vs. 6270 ng•h/mL, respectively), where a low-calorie meal was administered (minimum 100 kcal). Study JSBD indicates that a high fat intake might enhance bioavailability of merestinib; however, the mechanism remains unclear.

Human Metabolism and Excretion

The metabolic profile has been established in Study JSBC where healthy subjects (n=5) received a 120 mg dose of merestinib containing approximately 100 μCi of radioactivity in the form of ^{14}C-merestinib. The mean C_{max} was 544 ng/mL (22% CV), the median t_{max} was 4 hours, and the mean $t_{1/2}$ was 16.7 hours. The mean $AUC_{0-\infty}$ was 6930 ng•h/mL (46% CV), which is similar to that observed in cancer patients who received a dose of 120 mg. Following C_{max}, a secondary peak in total radioactivity was observed at approximately 10 hours in plasma and whole blood (and also for merestinib and its metabolite, LSN2800870 in plasma), which may suggest enterohepatic recirculation.

The main route of elimination was in the feces with a total mean (± standard deviation [SD]) of 96.2% (± 2.39%) of the dose excreted in the feces. Renal clearance is minimal (a mean [± SD] of 2.8% [± 0.461%] of the radioactivity was excreted in urine through the last collection interval).

Only approximately 14% of the dose is excreted as intact parent drug which indicates absorption of merestinib is almost complete. A total of 14 circulating metabolites were detected across plasma, urine, and feces, with parent drug and major metabolites M1 (LSN2800870) and M2 (LSN2887652) accounting for approximately 51%, 11%, and 18% of the circulating radioactivity, respectively. Merestinib is metabolized primarily through two routes, leading to the *N*-desmethyl metabolite LSN2800870, the hydroxymethyl metabolite LSN2887652, and M6, a product of both routes. These three metabolites account for 71% out of the 86% of the dose recovered in feces and urine as metabolites. These metabolites are believed to express similar biological activity as parent drug, but the relative potency is currently under evaluation.

Clinical Safety – Serious Adverse Events

As of 20 August 2015, a total of 57 serious adverse events (SAEs) in 37 patients have been reported. All were experienced by patients enrolled in Study JSBA. Six patients experienced a total of eight possibly study drug-related SAEs as assessed by the investigator or the sponsor. The events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) scale and included abdominal pain (grade 2), vomiting (grade 3), fatigue (grade 3), febrile neutropenia (grade 3), hyponatremia (grade 3), acute kidney injury (grade 3), and blood bilirubin increase (two events, both grade 3).

Table 5: Summary of SAEs in Study JSBA Considered Possibly Drug-Related

Preferred Term	Part B Colon / Rectum LY 120 mg N=20 n	Part B CCA LY 120 mg N=18 n	Part D CCA LY 80 mg + Cis 25 mg/m^2 N=17 n	Part E CCA LY 80 mg + Cis 25 mg/m^2 + Gem 1000 mg/m^2 N=6 n
Vomiting	1	0	0	0
Abdominal pain	1	0	0	0
Fatigue	1	0	0	0
Blood bilirubin increased	0	1	1	0
Hyponatremia	0	0	1	0
Kidney injury	0	0	1	0
Febrile neutropenia	0	0	0	1

Abbreviations: AE = adverse event; CCA = cholangiocarcinoma; CIS = cisplatin; Gem = gemcitabine; LY = merestinib; N = number of enrolled patients; n = number of patients with specified serious adverse event; SAE = serious adverse event;
Notes: Patients may be counted in more than 1 SAE.

During Study JSBA 30 deaths have been reported; 27 were considered related to disease progression. Three patients died due to AEs considered unrelated to the study drug (cardiac arrest, bacterial peritonitis, and liver failure). No study drug-related deaths have been reported in Study JSBA. No deaths occurred in Studies JSBC or JSBD.

Dose-Limiting Toxicities and Maximum Tolerated Dose

As of 20 August 2015, five dose-limiting toxicities (DLTs) were observed during the dose-escalation phase (Part A) of study JSBA. All five were due to reversible grade 3 increases in ALT and/or AST (1 of 10 patients at 120 mg, 2 of 12 patients at 160 mg, and 2 of 3 patients at 240 mg). A dose of 120 mg by mouth daily has been declared the recommended phase II monotherapy dose.

Of the 69 patients treated in Part B, five patients experienced a reversible grade 3 ALT and/or AST increase. One additional patient with CCA, status post bile duct stent and right percutaneous biliary catheter drain, experienced a reversible grade 3 increase in bilirubin and grade 1 increases in AST/ALT and was included in the DLT list. After 8 days of merestinib (120 mg), the patient was hospitalized with increased bilirubin and for persistent left duct dilatation. This patient was found to have a disease-related biliary tract obstruction which was treated with placement of a left biliary drain. The SAE was assessed by the investigators as related to the treated disease and possibly related to study drug treatment, since although the bilirubin level continued to improve, it did not return to baseline after drainage. The patient was removed from the study.

In Part C of the study (merestinib in combination with cetuximab in patients with HNSCC), one patient out of 20 experienced a reversible grade 3 increase in ALT while receiving the 120 mg dose. In Part D of the study, testing began at a dose of 120 mg merestinib with cisplatin 25 mg/m^2. One of the three patients treated at this dose level experienced a grade 3 increase in blood bilirubin and testing shifted to subsequently enroll patients to a lower dose of merestinib (80 mg daily with 25 mg/m^2 cisplatin). None of the 17 additional CCA patients who received the 80 mg dose were reported to have a DLT or DLT-equivalent event.

Based on available data, the increases in blood aminotransferase levels were reversible with treatment interruption followed by either dose reduction or treatment discontinuation.

Treatment-Emergent Adverse Events

Overall, 126 of the 166 patients (75.9%) treated in Study JSBA reported at least one treatment-emergent adverse event (TEAE). Across all study parts and grades, the most frequent TEAEs occurring in ≥ 10% of patients and believed to be related to study drug treatment were fatigue (25.9%), ALT increase (22.9%), AST increase (21.1%), nausea (18.1%), vomiting (11.4%), limb edema (10.8%), and alkaline phosphatase increase (10.2%).

Table 6: Treatment-Emergent Adverse Events Possibly Related to Merestinib Occurring in ≥ 5% of Patients Receiving the Phase II Dose of 120 mg or the Reduced Dose of 80 mg

CTCAE Term	All Grades N=82 n (%)	Grade ≥ 3 N=82 n (%)
Fatigue	24 (29.3)	3 (3.7)
Alanine aminotransferase increased	23 (28.0)	2 (2.4)
Edema limbs[a]	12 (14.6)	0
Aspartate aminotransferase increased	16 (19.5)	5 (6.1)
Nausea	11 (13.4)	0
Alkaline phosphatase increased	11 (13.4)	3 (3.7)
Vomiting	7 (8.5)	1 (1.2)
Anorexia	5 (6.1)	0 (0)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; N = number of enrolled patients; n = number of patients in category.
Note: no Grade 5 events were reported.
[a] Edema limbs includes lymphedema.

Three patients in Study JSBA discontinued treatment due to adverse events (AEs). These included AST increase, left ventricular systolic dysfunction, and blood bilirubin increase. The AE of left ventricular dysfunction occurred in the setting of antecedent concentric left ventricular hypertrophy in a patient who mistakenly increased his daily dose to a dose greater than was assigned. The AE of blood bilirubin increase in one patient occurred in the setting of a disease-related biliary tract obstruction. Consequently, the investigator assessed this event as related to both the biliary tract obstruction and study drug treatment.

In Study JSBC, one subject reported 2 AEs that were considered to be related to study drug; these included headache and flatulence, which were both mild in severity. No subject discontinued the study because of an AE.

In Study JSBD, of 23 subjects who received one or more doses of merestinib, nine TEAEs were reported that were related to merestinib as judged by the investigator. Overall, the most common TEAEs were headache (3 subjects), constipation (4 subjects), and raised liver enzymes, which

included ALT increase (3 subjects), AST increase (3 subjects), and GGT increase (2 subjects). All incidences of constipation and raised liver enzymes were considered to be related to study drug treatment, whereas the majority of headaches were considered to be unrelated. Most AEs were of mild severity with moderate AEs of ALT increase and AST increase reported in one subject each and one severe AE of ALT increase reported in one subject. Of the six patients who discontinued from the study, three discontinued due to AEs (elevated liver enzymes, chest discomfort, and elevated liver enzymes and increased platelet count), all of which (except platelet count increase) were related to study treatment. During the course of the study, three subjects experienced AEs related to elevations in liver enzymes following treatment with merestinib in the fed state, each of which were considered to be related to study treatment.

Efficacy

Due to the early phase of development of merestinib, comparative efficacy has not yet been demonstrated but will continue to be evaluated. In Study JSBA, 166 patients with advanced cancer have received merestinib. Among the 100 patients with measurable disease at baseline who have received ≥ 120 mg, 33 have had a best overall response of stable disease, with a median duration of 126 days (minimum = 43 days; maximum = 485 days). One confirmed complete response has been observed among the relapsed or refractory CCA patients who have received merestinib as an 80 mg once daily dose in combination with cisplatin in Part D. Among the 6 first-line CCA evaluable patients in Part E, one partial response and two stable disease responses have been observed.

2.3 Rationale

Identification of targetable genomic alterations in NSCLC has led to the development of effective small molecule inhibitors of mutated proteins such as *EGFR*, *ALK*, *ROS1*, and *BRAF*. Mutations in *MET* exon 14 occur in approximately 3% of NSCLCs[7], and these cancers are sensitive to treatment with c-Met inhibitors such as crizotinib; however, there are no FDA-approved drugs for this mutational subset of lung cancers. Furthermore, mechanisms of resistance to these drugs have not yet been described, and it is not known if treatment with a different *MET* inhibitor can overcome resistance to drugs like crizotinib[2-4,19,20]. Merestinib is a potent oral *MET* inhibitor which has already been evaluated in a phase I clinical trial[11,18,21].

Inhibition of the additional oncokinase targets of merestinib has the potential to demonstrate anti-cancer effects in non-*MET* mutated cancers as well. Rearrangements in *NTRK* have been described in lung cancer and other solid tumor malignancies, and these cancers appear to respond to *NTRK* inhibitors such as LOXO-101. Similarly, there are no approved agents for cancers with *NTRK* alterations and mechanisms of resistance to *NTRK* inhibitors have also not been reported[8,22].

2.4 Correlative Studies

Fresh Tumor Tissue Biopsies

NSCLCs harboring somatic mutations in kinases are often sensitive to small molecule kinase inhibitors. For example, crizotinib, an ALK/ROS1/MET inhibitor is approved for use in NSCLC and has antitumor activity in NSCLCs with genomic alterations in ALK, ROS1, and MET. Unfortunately, the efficacy of these kinase inhibitors has been limited by the invariable development of acquired drug resistance. The identification of resistance mechanisms has been instrumental in the development of strategies aimed at preventing or overcoming resistance[23]. In the case of ALK-rearranged NSCLC, a greater understanding of the various mechanisms of resistance to crizotinib has led to the approval of several next generation ALK inhibitors that are able to overcome resistance[24].

In order to retrospectively explore the determinants of response and resistance to merestinib, a mandatory fresh tumor biopsy will be obtained from patients who enroll on trial who have received a prior *MET* or *NTRK* inhibitor. Biopsy samples will be submitted for Next Generation Sequencing (NGS) at the Center for Advanced Molecular Diagnostics (CAMD) at Brigham and Women's Hospital to determine mechanisms of resistance to prior TKIs, including the development of alternate kinase domain mutations or bypass signaling tract activation. These results will be correlated with clinical outcome to investigate whether merestinib can overcome certain resistance mechanisms. This testing will further identify the characteristics of patients who respond to treatment with merestinib versus patients that do not, helping with future selection of patient populations appropriate for treatment with *MET* or *NTRK* inhibitor therapy.

In addition, patients will be offered an optional biopsy at the time of progression if deemed safe and feasible by the treating investigator. This tissue will also be submitted for targeted sequencing and NGS to identify genetic mechanisms of resistance. The testing will help with both the creation and selection of future treatment strategies following the development of resistance to merestinib.

Patients undergoing a biopsy either prior to starting merestinib or at the time of disease progression will be given the option to have tissue sent to the Dana-Farber Cancer Institute Translational Research Laboratory under the team of Dr. Pasi Jänne for development of patient-derived cell lines and mouse xenograft models. There are few available cell lines harboring *MET* exon 14 mutations or *NTRK* rearrangements. These patient-derived samples will be extremely valuable for testing various drugs or drug combinations both *in vitro* and *in vivo*.

Quantitative Non-Invasive Genotyping

Analysis of circulating free DNA for identification of activating mutations/rearrangements in *MET* and *NTRK* as well as resistance mutations will be conducted. This data will be correlated with clinical outcome to identify indicators of sensitivity or resistance. Using digital PCR techniques, the Belfer Center at the Dana-Farber Cancer Institute has designed methods to quantitatively evaluate the levels of circulating free plasma DNA. Tumor DNA is preferentially identified by selecting for key oncoproteins which would only be present in the tumor genome (such as activating mutations/rearrangements in *MET* or *NTRK*). Previously, this methodology was developed for important *EGFR* mutations (del 19, L858R and T790M), *KRAS* (four most common mutations), and *BRAF* (V600E). The Belfer Center has demonstrated that levels of tumor DNA will decline longitudinally over time if there is a response to the treatment

administered. To further assess this concept, plasma will be collected from participants to evaluate whether circulating free plasma DNA declines or increases with the administration of merestinib in *MET* and *NTRK* mutant/rearranged tumors in patients who either respond or progress on therapy. Plasma samples will also be evaluated for detection of possible resistance mutations (e.g., kinase domain mutations or bypass tract activation).

3. PARTICIPANT SELECTION

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy, with the exception of the informed consent and baseline tumor imaging which may be obtained up to 28 days prior to the start of protocol therapy.

3.1 Eligibility Criteria

3.1.1 For enrollment into the *MET* cohort: Participants must have a histologically or cytologically confirmed advanced NSCLC and must have received at least one prior line of therapy in the metastatic setting.

3.1.2 For enrollment into the *NTRK* cohort: Participants must have a histologically or cytologically confirmed advanced solid tumor and must have received at least one prior line of therapy in the metastatic setting.

3.1.3 Participants enrolling into the *MET* cohort must have a *MET* exon 14 mutation as confirmed by targeted NextGen Sequencing using the DFCI/BWH OncoPanel or another CLIA-certified method. Participants whose NSCLC specimens contain actionable genetic mutations/alterations (e.g. *ALK/EGFR*) should receive appropriate targeted therapies prior to enrollment in the trial.

3.1.4 Participants enrolling into the *NTRK* cohort must have an *NTRK1, 2,* or *3* rearrangement as confirmed by targeted NextGen Sequencing using the DFCI/BWH OncoPanel or another CLIA-certified method.

3.1.5 Participants must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as $\geq$ 20 mm with conventional techniques or as $\geq$ 10 mm with spiral CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease.

3.1.6 Participants enrolling to the *MET* cohort who have received treatment with a prior *MET* inhibitor must be able and willing to undergo a baseline tumor biopsy.

3.1.7 Participants enrolling to the *NTRK* cohort who have received treatment with a prior *NTRK* inhibitor must be able and willing to undergo a baseline tumor biopsy.

3.1.8 Age ≥ 18 years. As no dosing or adverse event data are currently available in participants < 18 years of age, children are excluded from this study but will be eligible for future pediatric trials.

3.1.9 ECOG performance status ≤ 1 (see Appendix A).

3.1.10 Participants must have normal organ and marrow function as defined below:

– Absolute neutrophil count	≥ 1.5 K/uL
– Platelets	≥ 100 K/uL
– Hemoglobin	≥ 9 g/dL (with or without transfusion support)
– Total bilirubin	≤ 1.5 × institutional upper limit of normal (ULN)
– AST(SGOT)/ALT(SGPT)	≤ 2.5 × institutional ULN, unless liver metastases are present and then ≤ 5 × institutional ULN is acceptable
– Serum creatinine	≤ 1.5 × institutional ULN

3.1.11 The effects of merestinib on the developing human fetus are unknown. For this reason and because *MET* inhibitor agents are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of merestinib administration.

3.1.12 Ability to understand and the willingness to sign a written informed consent document.

3.1.13 Participants must be able to swallow and retain oral medication or have an enteral feeding tube in place for study drug administration.

3.1.14 Participants who have received prior oral tyrosine kinase inhibitors (TKIs) will be allowed on study if at least 5 half-lives have elapsed since the date of their last dose of TKI.

3.2 Exclusion Criteria

3.2.1 Participants who have had chemotherapy, immune therapy, other investigational therapy, major surgery, or radiotherapy within 3 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study.

3.2.2 Participants who have not recovered to eligibility levels from adverse events due to agents administered prior to study entry.

3.2.3 Participants who are receiving any other investigational agents.

3.2.4 Participants with untreated brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. Participants with a history of brain metastases that have been treated, are no longer taking corticosteroids, and have been stable on imaging for ≥ 4 weeks following the last date of treatment are permitted. Note: a brain MRI is required during the screening period.

3.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to merestinib.

3.2.6 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.7 Pregnant women are excluded from this study because merestinib is an agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with merestinib, breastfeeding should be discontinued if the mother is treated with merestinib.

3.2.8 Known HIV-positive participants are ineligible because these participants are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in participants receiving combination antiretroviral therapy when indicated.

3.2.9 Participants enrolling to the *MET* cohort who have received a prior *MET* inhibitor may not be on anticoagulant therapy unless the investigator has deemed it safe to temporarily hold to facilitate the baseline tumor biopsy.

3.2.10 Participants enrolling to the *NTRK* cohort who have received a prior *NTRK* inhibitor may not be on anticoagulant therapy unless the investigator has deemed it safe to temporarily hold to facilitate the baseline tumor biopsy.

3.2.11 Participants with uncontrolled high blood pressure, defined as a blood pressure during screening of ≥ 160/100 despite medical management.

3.2.12 Participants must not have any clinically significant gastrointestinal abnormalities that in the opinion of the treating investigator may alter absorption of oral medications, such as malabsorption syndrome or major resection of the stomach or bowels.

3.2.13 Participants with a history of a second primary malignancy. Exceptions include: patients with a history of malignancies that were treated curatively and have not recurred within 3 years prior to study entry; resected basal and squamous cell carcinomas of the skin, and completely resected carcinoma *in situ* of any type.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

5. TREATMENT PLAN

5.1 Treatment Regimen

Participants will take merestinib at the recommended phase II dose of 120 mg by mouth daily. Patients will take merestinib continuously through the 28 day treatment cycle. Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy, with the exception of palliative radiation therapy to non-target lesions when pre-approved by the principal investigator. Treatment with bisphosphonates will be permitted.

Participants will be requested to maintain a study medication diary that will indicate each dose of medication taken to illustrate treatment compliance. The medication diary should be returned to appropriate research staff for review at the end of each treatment cycle.

5.2 Pre-Treatment Criteria

5.2.1 Cycle 1, Day 1

Patients who completed screening assessments > 72 hours prior to cycle 1 day 1 should have cycle 1 day 1 laboratory values that re-meet eligibility criteria. If screening assessments were completed ≤ 72 hours prior to cycle 1 day 1, laboratory tests do not need to be repeated on cycle 1 day 1 and the screening laboratory values can be used as the cycle 1 day 1 values.

5.2.2 Start of Subsequent Cycles

To be eligible to begin subsequent cycles of treatment, toxicity considered at least possibly related to merestinib must have recovered to ≤ grade 2 or baseline. Management of specific toxicities considered at least possibly related to merestinib are outlined in Section 6.1.

5.3 Agent Administration

5.3.1 Merestinib

Participants will take merestinib at the recommended phase II dose of 120 mg by mouth daily. Merestinib should be taken with food or within one hour of a meal. Doses of merestinib should be taken approximately 24 hours apart, there is a +/- 4 hour dosing window. Doses that would be outside of this time range should be considered missed and should not be taken. Vomited doses should not be retaken. Tablets of merestinib should be swallowed whole and should not be chewed or crushed (unless administered via feeding tube).

All persons should be instructed to wash their hands after handling the study drug tablets.

Administration via Feeding Tube

Merestinib tablets may be prepared for administration per enterostomy feeding tubes. Tablets corresponding to the appropriate dose should be crushed with an Ezy Dose Tablet Crusher (or an equivalent device) and prepared into a slurry with the addition of 10 mL of water in the device. The resulting tablet slurry should be transferred to the feeding tube using a syringe ensuring that all contents are transferred. Crushing device and syringe should be flushed with additional small quantities of water (~25 mL). Rinsing may be repeated to ensure transfer of all tablet contents. The total volume of water used should not exceed 100 mL. Tablet slurry should be administered via the feeding tube within 4 hours of slurry preparation. With use of this technique, non-clinical testing has demonstrated recovery of ≥ 97.6% of merestinib.

Administration Guidelines

Administration of merestinib may cause minor changes in heart rate and blood pressure.

During clinical study participation patients should be carefully monitored as described in the Study Calendar in Section 10.

Due to the potential for changes in vasculature in actively growing bone observed in non-clinical studies, careful monitoring of bone repair and healing may be warranted in individuals who incidentally develop bone fractures or injuries through trauma, surgery, or other means.

5.4 General Concomitant Medication and Supportive Care Guidelines

Investigators should use appropriate supportive medications to address toxicities that arise during the study, including but not limited to antiemetics, antidiarrheals, and blood product transfusion.

It is recommended that strong CYP3A4 inhibitors and inducers be avoided within 2 weeks before the start of study drug treatment and for the duration of trial treatment unless medically necessary. In addition, merestinib may increase the concentrations of P-gp substrates, and increased monitoring is recommended for patients taking digoxin.

Based on the available non-clinical data, there is a possible risk of clinical DDIs when merestinib is co-administered with substrates of cytochrome P450 (CYP)2C8, CYP2C9, and CYP2C19. In the absence of more data to refine the risk of interaction, caution is warranted in the concomitant use of merestinib with CYP2C8, CYP2C9, and CYP2C19 substrates known to have a narrow therapeutic range (e.g., warfarin, phenytoin, tricyclic antidepressants, tolbutamide, etc.). When, in the clinical investigator's opinion, concomitant use of these medications is indicated, use of these agents should be carefully monitored.

The chemical structure of merestinib is consistent with the potential for photosensitivity. While photosensitivity has not been reported among patients who have received merestinib, patients should be advised to minimize or avoid exposure to strong sunlight, sunlamps, or other sources of ultraviolet radiation for long periods of time and are advised to use sunscreen and sunglasses.

5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression, and tolerance. In the absence of treatment delays due to adverse events, treatment may continue indefinitely or until one of the following criteria applies:

- Disease progression (unless the participant is exhibiting clinical benefit as agreed upon with the principal investigator)
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)

- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- Pregnancy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

For Centralized Subject Registrations, the research team submits a completed Off Treatment/Off Study form to ODQ when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Mark Awad MD, PhD at 617-632-3468.

5.6 Duration of Follow Up

Participants will be followed until death after removal from protocol therapy. This follow up will be performed by review of the medical record, contact with care providers, and/or telephone contact as needed every 3-4 months.

5.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

For Centralized Subject Registrations, the research team submits a completed Off Treatment/Off Study form to ODQ when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

6. DOSING DELAYS/DOSE MODIFICATIONS

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.03 can be downloaded from the CTEP website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

6.1 Specific Toxicity Management

Dose delays and modifications due to toxicity considered at least possibly related to merestinib will be made as indicated in the following tables:

Table 7: AST/ALT Management	
AST (SGOT) and/or ALT (SGPT) Increase	**Merestinib Management**
≤ Grade 2	No change.
Grade 3, *increase lasting less than 8 days*	Hold study medication until resolution to ≤ grade 1 or baseline. Resume study medication at the same dose level.
Grade 3, *increase lasting 8 or more days* ***-OR-*** **Grade 4**	Hold study medication until resolution to ≤ grade 1; resume study medication with one dose level reduction.
AST and/or ALT > 3 × the institutional ULN *AND* total bilirubin ≥ 2 × the institutional ULN	Permanently discontinue merestinib therapy.

As a precaution, patients with baseline elevation of hepatic transaminases or with increasing (compared with baseline) hepatic transaminases during merestinib therapy should be monitored closely for evidence of progressive hepatic injury and disease-associated biliary obstruction. In addition, as merestinib is anticipated to be predominately metabolized by the liver with biliary excretion of its metabolites, patients with reduced hepatic function may exhibit decreased clearance of merestinib.

Table 8: Nausea Management	
Nausea	**Merestinib Management**
≤ Grade 2	No change.* Implement appropriate supportive care (e.g., antiemetics) as clinically indicated.
≥ Grade 3, *not optimally managed*	Hold study medication and implement appropriate supportive care (including antiemetics and IV hydration if indicated). Upon resolution to ≤ grade 2, resume study medication at the same dose level.

≥ Grade 3, *optimally managed*	Hold study medication until resolution to ≤ grade 2; resume study medication with one dose level reduction.
**If a patient is experiencing intolerable grade 2 nausea despite optimal medical management, their study medication may be held at the treating investigator's discretion. Upon resolution to grade 1 or baseline, the study medication can be dose reduced at the treating investigator's discretion.*	

Table 9: Management of Vomiting	
Vomiting	**Merestinib Management**
≤ Grade 2	No change.* Implement appropriate supportive care (e.g., antiemetics) as clinically indicated.
≥ Grade 3, *not optimally managed*	Hold study medication and implement appropriate supportive care (including antiemetics and IV hydration if indicated). Upon resolution to ≤ grade 1, resume study medication at the same dose level.
≥ Grade 3, *optimally managed*	Hold study medication until resolution to ≤ grade 1; resume study medication with one dose level reduction.
**If a patient is experiencing intolerable grade 2 vomiting despite optimal medical management, their study medication may be held at the treating investigator's discretion. Upon resolution to grade 1 or baseline, the study medication may be dose reduced at the treating investigator's discretion.*	

Table 10: Fatigue Management	
Fatigue	**Merestinib Management**
≤ Grade 2	No change.*
≥ Grade 3	Hold study medication. Upon resolution to ≤ grade 2, resume study medication with one dose level reduction.
**If a patient is experiencing intolerable grade 2 fatigue, their study medication may be held at the treating investigator's discretion. Upon resolution to grade 1 or baseline, the study medication can be dose reduced at the treating investigator's discretion.*	

Table 11: Management of Other Toxicity	
Other Toxicity	**Merestinib Management**
≤ Grade 2	No change.*
≥ Grade 3	Hold study medication. Upon resolution to ≤

	grade 2, resume study medication with one dose level reduction.
**If a patient is experiencing intolerable grade 2 toxicity, their study medication may be held at the treating investigator's discretion. Upon resolution to grade 1 or baseline, the study medication can be dose reduced at the treating investigator's discretion.*	

6.2 Treatment Delays

Participants who are benefiting from merestinib in the opinion of the treating investigator may have their study medication held for up to 4 weeks to allow for recovery of toxicity. Participants requiring a longer hold should be removed from the trial. Exceptions to this requirement are possible should the principal investigator agree that the patient may continue despite the length of time off drug.

If the study medication is placed on hold for toxicity, the counting of cycle days and pre-planned assessment schedule will continue without interruption. For example, a patient who does not receive their cycle 3 day 15 – cycle 3 day 19 doses of merestinib due to toxicity would restart on cycle 3 day 20 and will proceed with their next regularly scheduled visit (cycle 4 day 1). Additional interim visits can be conducted as clinically necessary to manage toxicity; however once resolved, the cycle will not restart for dosing delays due to toxicity. Exceptions to this are possible after discussion with the principal investigator.

6.3 Dose Modifications

A maximum of one dose reduction is allowed. If a patient requires more than one dose reduction, they should be removed from the trial. Once a patient's dose has been reduced, it must be maintained at the reduced dose and it cannot be re-escalated.

Table 12: Dose Modifications

Dose Reduction Level	Merestinib Dose
-1	80 mg Daily

6.4 Overdose Management

There is no known antidote for over-dosage of merestinib. In case of suspected overdose, monitor hematology, chemistry, and vital signs and give supportive care as necessary.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in**

addition to routine reporting.

7.1 Expected Toxicities

7.1.1 Adverse Events List

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 2.2.2, in Table 6, and in the investigator's brochure (IB). Fatigue has been the most frequent toxicity following treatment with merestinib, followed by elevation in hepatic transaminases.

Elevation in liver transaminases (AST and/or ALT) were noted to occur in patients at the highest tested dose levels of merestinib, and these events defined the upper range of dose testing. Although the grade 3 changes in transaminases tended to occur at higher exposures, no direct relationship between these events and merestinib exposure was noted. Of the 69 patients given merestinib at the recommended phase II dose in the monotherapy expansion of the phase I trial, eight patients experienced a reversible grade 3 ALT and/or AST increase. Based on available data, these changes were reversible with treatment interruption followed by either dose reduction or treatment discontinuation.

For the purposes of suspected unexpected serious adverse reaction (SUSAR) reporting, there are no adverse drug reactions listed for merestinib; therefore any serious adverse event deemed related to merestinib will be reported as a SUSAR per local regulatory requirements.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - Expedited reporting of AEs for merestinib should be done only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided or if it fits under the definition of a Serious Adverse Event defined in Section 7.3.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Serious Adverse Events

A serious adverse event (SAE) is any adverse event that occurs following the initiation of study treatment that results in one of the following outcomes:

- Death
- Hospitalization for greater than 24 hours
- Prolonging an existing inpatient hospitalization
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Considered significant by the investigator for any other reason

Previously planned (prior to signing the informed consent form) surgeries, and non-disease related elective surgeries planned during the course of the study, should not be reported as SAEs unless the underlying medical condition has worsened or appeared during the course of the study.

Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs. Events that occurred prior to the first dose of study treatment should not be reported as SAEs.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Death due to disease progression should not be reported as an SAE unless the investigator deems it to be related to the use of study drug.

Study site personnel must alert Eli Lilly of any SAE as soon as possible and no later than 24 hours of the investigator and/or institution receiving notification of the SAE experienced by a patient participating in the study. The SAEs should be reported using a standard SAE reporting form (e.g. CIOMS form, Medwatch 3500a form, or similar). The SAE reports are to be sent to Eli Lilly via fax at 1-866-644-1697.

7.3.1 Investigators **must** report to the Overall PI any SAE that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.4 Expedited Adverse Event Reporting

7.4.1 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

7.5 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.6 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.7 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

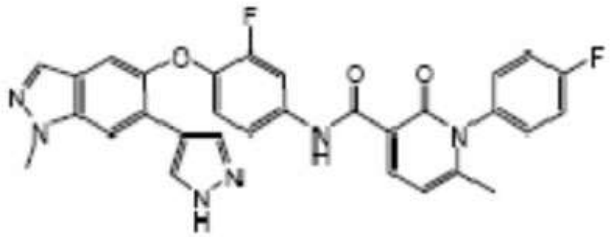
A list of the adverse events and potential risks associated with the investigational administered in this study can be found in Section 7.1.

8.1 Merestinib (LY2801653)

8.1.1 Physical and Chemical Characteristics

Chemical Name: N-(3-fluoro-4-(1-methyl-6-(1*H*-pyrazol-4-yl)-1*H*-indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide

Chemical Structure:



Molecular Weight: 552.5

Molecular Formula: $C_{30}H_{22}F_2N_6O_3$

Physical Description: White solid

pKa: 1.61 (in water)

pH: 6.82 (water slurry at 2 mg/mL concentration)

Solubility: < 0.001 mg/mL in water
0.340 mg/mL in methanol
1.560 mg/mL in ethanol

8.1.2 **Form**

Merestinib (LY2801653) is supplied for clinical trial use as tablets. The beige tablets are composed of merestinib and the inactive ingredients hydroxypropyl methylcellulose acetate succinate, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, sodium lauryl sulphate, colloidal silicon dioxide, magnesium stearate, and Opadry® II Tan. Each tablet contains merestinib equivalent to 40 or 80 mg of the base compound.

In addition 40 mg blue nonagon tablets may be supplied that are composed of merestinib and the following inactive ingredients: silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, mannitol, microcrystalline cellulose, sodium lauryl sulfate, sodium stearyl fumarate. The proprietary color mix contains blue hypromellose, titanium dioxide, triacetin, and FD&C Blue 2 indigo carmine.

8.1.3 **Storage and Stability**

Merestinib (LY2801653) is stable when stored at room temperature, defined as 10˚C - 30˚C (50˚F to 86˚F).

The investigator or pharmacist will ensure that all investigational products are stored in a secure area, under recommended storage conditions and in accordance with applicable regulatory requirements. The site should monitor the minimum and maximum temperature and maintain temperature logs to confirm the correct storage of all

investigational products used in the trial.

8.1.4 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment. Anyone who handles merestinib tablets should be instructed to wash their hands following contact.

8.1.5 Availability

Merestinib (LY2801653) is an investigational agent that will be supplied by Eli Lilly and Company.

8.1.6 Administration

Participants will take merestinib at the recommended phase II dose of 120 mg by mouth daily. Patients will take merestinib continuously through the 28 day treatment cycle. Treatment will be given on an outpatient basis.

Merestinib should be taken with food or within one hour of a meal. Doses of merestinib should be taken approximately 24 hours apart, there is a +/- 4 hour dosing window. Doses that would be outside of this time range should be considered missed and should not be taken. Vomited doses should not be retaken. Tablets of merestinib should be swallowed whole and should not be chewed or crushed (unless administered via feeding tube, please see Section 5.3 for guidance on feeding tube administration).

8.1.7 Ordering

Drug supply will be ordered from Eli Lilly by site pharmacy personnel.

8.1.8 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.9 Destruction and Return

Expired supplies of merestinib should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form. At the end of the study, unused supplies of merestinib should also be destroyed according to institutional policies and destruction will be documented in the Drug Accountability Record Form.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Exploratory Pharmacodynamic Tumor Biopsies

9.1.1 OncoPanel Testing (All Participants)

A mandatory fresh tumor biopsy will be obtained from patients enrolling to the trial who have received a prior *MET* or *NTRK* inhibitor, as described in Section 2.4 – Correlative Studies. The biopsy is to be obtained at baseline (prior to the first dose of study medication).

An optional biopsy will be offered at the time of disease progression if judged by the treating investigator to be safe and feasible. Preferably, time of progression biopsies should be obtained prior to the initiation of another cancer treatment. However, in the event that it is not possible to perform the biopsy before another treatment is begun, biopsies can be obtained up to 30 days after the last dose of merestinib.

Whenever possible, core biopsy samples should be collected for analysis. Three-to-four biopsy passes utilizing a 16-18 gauge needle are preferable, but 20 gauge core needle biopsies are also acceptable at the discretion of the interventionalist performing the biopsy procedure.

If a core biopsy is judged to be too unsafe or difficult for the participant in the opinion of the treating investigator, a fine needle aspirate (FNA) or cytology sample can also be collected. The goal for a thoracentesis or paracentesis procedure will be 500 – 1000 mL collected in a standard collection tube. The goal for an FNA will be three distinct passes. Less than the goal amount of tissue is acceptable for any of the biopsy collection methods, and should be based upon the clinical judgment of the treating investigator and the clinician performing the procedure.

Handling of samples for NGS/OncoPanel testing:

- Samples should be formalin-fixed and paraffin embedded (FFPE) per routine local procedures.
- A minimum of 10 unstained slides and 1 H&E slide of 5 – 10 micron thickness should be labeled with the protocol number, study subject number, and the date of sample collection.
- Blocks should not be sent to CAMD for analysis, blocks should be processed into slides prior to shipment.
- Samples should be sent to the Center for Advanced Molecular Diagnostics (CAMD) at Brigham and Women's Hospital for performance of the NGS with the specimen drop-off form:

  Center for Advanced Molecular Diagnostics
  Brigham & Women's Hospital
  Shapiro Cardiovascular Building
  70 Francis Street, 5th Floor
  Boston, MA 02115

9.1.2 Optional Generation of Cell Lines and Xenograft Models (DFCI Participants Only)

Optionally and if enough tissue remains, one-to-two biopsy passes should be placed in PBS per standard procedures. The sample should be labeled with the protocol number, subject number, and the date of sample collection. The samples should be sent to the Dana-Farber Cancer Institute Translational Research Laboratory for generation of cell lines and xenograft models at:

360 Longwood Avenue
4th floor, LC-4101
Boston, MA 02215

9.2 Plasma Genotyping Correlative Studies (All Participants)

Plasma will be collected from patients at the following intervals:

- Anytime pre-dose on Cycle 1 Day 1
- On the first day of each subsequent cycle*
- At the off study visit

**After completion of cycle 6, plasma can be collected on day 1 of every odd cycle – coinciding with restaging scan visits (i.e., Cycle 7 day 1, Cycle 9 day 1, Cycle 11 day 1, and so on).*

The exact date and time of every sample should be recorded.

Plasma collection protocol
NOTE: Time period from draw to freezing of plasma must be less than 3 hours.

1. Draw venous blood into one (1) 10 mL EDTA tubes labeled CFDNA and immediately gently invert the tubes 8-10 times. Write the patient and draw date number on the tube.

2. Immediately centrifuge for 10 minutes at 1500 (+\- 150) x g. NOTE: Brake switch must be off so the cell/plasma interface is not disturbed.

3. Pipette the plasma layer into a 15 mL tube labeled “CFDNA/with patient #”. Do not ship. NOTE: Do not dip the tip of the pipette into the plasma/cell interface. Leave a thin plasma layer intact over the interface.

4. Centrifuge the 15 mL tube containing the plasma only for 10 minutes at 3000 (+/- 150) x g.

5. Transfer using a fresh pipette, the supernatant into a second 15 mL tube labeled “CFDNA super.do not ship”. NOTE: Leave about 0.3 mL of supernatant in the centrifuged 15 mL tube. This leftover 0.3 mL contains cellular debris.

6. Using a fresh pipette, transfer 1 mL of plasma from the “super.do not ship” tube into max four (4) 2 mL cryovials labeled CFDNA.ship.patient#/

7. Freeze immediately upright at -70ºC or colder until shipping.

Samples should be sent on dry ice to:

Julianna Supplee
Translational Research Laboratory
Belfer Center for Applied Cancer Research
360 Longwood Avenue LC-4202
Boston, MA 02215
617-582-8723
Julianna_supplee@dfci.harvard.edu

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy, with the exception of the informed consent and baseline tumor imaging which may be obtained up to 28 days prior to the start of protocol therapy.

Assessments must be performed prior to administration of any study agent.

Table 13: Study Calendar

	Pre-Study[A]	Cycle 1 Day 1	Cycle 1 Day 15[B]	Cycles 2+ Day 1[C]	End of Treatment[D]	Every 3 Months after Discontinuing[E]
Informed consent	X					
Demographics	X					
Medical history	X					
Physical exam[F]	X	X	X	X	X	
Vital signs[G]	X	X	X	X	X	
Height	X					
Weight	X	X		X	X	
ECOG performance status	X	X		X	X	
CBC w/diff, plts	X	X	X	X	X	
Serum chemistry[H]	X	X	X	X	X	
Adverse event evaluation		X----------X			X	
Radiologic evaluation	X	CT or MRI imaging of any disease-involved site. Radiologic measurements should be performed at			X	

Table 13: Study Calendar

	Pre-Study[A]	Cycle 1 Day 1	Cycle 1 Day 15[B]	Cycles 2+ Day 1[C]	End of Treatment[D]	Every 3 Months after Discontinuing[E]
		the end of cycle 2 (cycle 2 day 28) and at the end of every 2 cycles of treatment thereafter (i.e., cycle 4 day 28, cycle 6 day 28, and so on). There is a +/- 7 day window on imaging evaluations.				
Brain MRI	X	Repeat brain imaging as clinically indicated.				
Serum β-HCG[I]	X				X	
Merestinib[J]		X		X		
Fresh Tumor Biopsy[K]	X				X	
Plasma Genotyping[L]		X		X	X	
Telephone or Care Provider Contact						X

A. Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy, with the exception of the informed consent and baseline tumor imaging which may be obtained up to 28 days prior to the start of protocol therapy.
B. Cycle 1 Day 15 has a +/- 3 day scheduling window to accommodate adverse weather, holidays, vacations, etc.
C. The start of a subsequent cycle may be delayed by up to 7 days for scheduling issues (vacations, holidays, adverse weather, etc.). Following completion of cycle 6, at the treating investigator's discretion clinic visits may occur every other cycle.
D. End of treatment evaluation to be completed within 30 days of the last dose of study medication. Note: follow up visits or other contact is required in order to identify SAEs during the 30 days following the end of study treatment.
E. Participants will be followed until death or withdrawal of consent after removal from protocol therapy. This follow up will be performed by review of the medical record, contact with care providers, and/or telephone contact as needed every 3-4 months.
F. Routine physical exam. Screening physical exam should include a neuromuscular examination with focus on monitoring for tremors.
G. Vital signs to include heart rate, blood pressure, temperature, respiratory rate, and oxygen saturation (O_2 sat).
H. Sodium, potassium, chloride, CO_2, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, SGOT [AST], SGPT [ALT], and globulin. Other tests may be ordered as clinically indicated.
I. Serum pregnancy test only required for women of childbearing potential. Childbearing potential defined as any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months; or women with a documented plasma follicle-stimulating hormone level >35μlU/mL).
J. Merestinib to be taken daily as described in Section 5.3. Adequate supply should be dispensed at the beginning of each new cycle to accommodate any pre-planned scheduling delays.
K. A fresh tumor biopsy is required at baseline from patients who have received prior therapy with a *MET* or *NTRK* inhibitor. An optional biopsy at the time of disease progression will be offered to any patient. Please see Section 9 for more detail.
L. Plasma genotyping sample to be obtained anytime pre-dose on Cycle 1 Day 1. The exact time of the sample should be recorded. Additional samples to be collected at any time on the first day of each subsequent cycle (the exact time of the sample should be recorded) and at the off study visit. Please see Section 9 for more detail.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every approximately every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area may not be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT

scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

(a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

(b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast),

then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

MIBG (meta-iodobenzylguanidine).The following is recommended, to assure high quality images are obtained.

Patient preparation: Iodides, usually SSKI (saturated solution of potassium iodide), are administered to reduce thyroidal accumulation of free radioiodine, preferably beginning the day prior to injection and continuing for 3 additional days (4 days total). For infants and children, one drop t.i.d. is sufficient, for adolescents 2 drops t.i.d., and for adults 3 drops t.i.d. Participants and/or parents are asked about exposure to potential interfering agents. If none is noted, an indwelling intravenous line is established. The dose of MIBG is administered by slow intravenous injection over 90 seconds.

Images from the head to the distal lower extremities should be obtained.

I-123MIBG scintigraphy is performed to obtain both planar and tomographic images.

Planar: Anterior and posterior views from the top of the head to the proximal lower extremities are obtained for 10 minutes at 24 hours and occasionally at 48 hours following injection of 10 mCi/1.7 square meters of body surface area (~150 μCi/kg, maximum 10 mCi). Anterior views of the distal lower extremities are adequate. A large field of view dual head gamma camera with low energy collimators is preferred.

SPECT: Most participants receiving I-123 MIBG also undergo SPECT at 24 hours, using a single or multi-headed camera with a low energy collimator. The camera is rotated through 360 degrees, 120 projections at 25 seconds per stop. Data are reconstructed using filtered back projections with a Butterworth filter and a cut off frequency of 0.2-0.5. SPECT/CT may be performed at institutions with this capacity.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later data and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.1.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.3.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.3.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-	No	SD	Documented at least once ≥4

	PD/not evaluated			wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.5 Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

11.1.6 Response Review

Evaluation of scans will be done centrally at the DFCI using the Tumor Metrics Core.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date

participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

13. STATISTICAL CONSIDERATIONS

This is a single arm phase II study examining the anti-tumor activity of merestinib in patients with advanced cancer exhibiting a *MET* exon 14 mutation. The primary goal of the study will be to examine the ORR utilizing RECIST 1.1 criteria in patients harboring *MET* mutations following administration of merestinib. Secondary efficacy measures will include assessment of the safety and tolerability of merestinib in both *MET* and *NTRK* patients, as well as the OS rate, the PFS rate, and the DoR in patients with tumors harboring *MET* mutations.

A total of 14 patients with *MET* exon 14 mutations will be enrolled in the first stage of a Simon 2-stage design. If three or more responses are observed an additional six patients will be enrolled, for a total of 20 patients. If two or fewer responses are observed among the first 14 patients, the study will close for lack of efficacy. Merestinib will be deemed promising if a total of four or more responses are observed among all 20 patients. This design has an 84% chance of stopping early under the null, and has an 86% power to detect a response rate of 32% while testing at the one-sided 0.10-level against the historical control rate of 10%.

An additional 5 patients with an *NTRK1, 2,* or *3* rearrangement will be enrolled to a separate exploratory group. As *NTRK* rearrangements are rare and a large cohort may be difficult to fill, the initial substudy is planned to look at a small number of patients. If responses are observed, a larger multi-center study may then be undertaken. Additionally if the *MET* cohort is found promising and the cohort fills to capacity (20 patients) prior to the *NTRK* cohort filling, the remaining *NTRK* slots may be re-distributed to allow more participants to enroll to the *MET* cohort at the principal investigator's discretion. For example, if 20 participants have enrolled to the *MET* cohort and the treatment is considered promising (with four or more responses) but only three participants have been enrolled to the *NTRK* cohort, the remaining two *NTRK* slots may be shifted to enroll an additional two participants with *MET* exon 14 mutations instead (bringing the total *MET* enrollment to 22). The intent behind this is to avoid difficulties with slow accrual prolonging the overall duration of the trial.

The exploratory endpoints for the *NTRK* cohort will include the ORR, OS, PFS, and DoR in patients with advanced cancer harboring an *NTRK* rearrangement. Among this cohort of 5 patients with *NTRK* rearrangements, if the cohort fills to capacity there is a 0.83 probability that we observe at least 1 response if the true but unknown response rate associated with merestinib is 30%. In reality, if the associated response in this population is low (3%), then the probability that we observe at least 1 response in this cohort is low (0.14).

For the analysis of the response efficacy measures among both the *MET* and *NTRK* groups,

participants will be censored if they are alive and without disease progression at the date of the last disease evaluation. In the case of OS, participants will be censored if they are living at the date last known alive.

Statistical Analysis Plan for Correlative Studies:

The role of the diagnostic specimen is identification of mutations for the purpose of enrollment onto this trial; however, when paired with genomic results obtained from the biopsy at progression, it is of interest to identify new alterations that were not present at baseline. Initial analyses of these data will utilize tests for association comparing the frequency of a particular genomic aberration at baseline and at progression (for example, using McNemar's test) and association between alterations and baseline characteristics (for example, using Fisher's exact test). More sophisticated analyses may include multivariable logistic regression modeling and/or competing risks analysis, however it is expected that analyzable results will not be obtained from 100% of patients (either due to things like assay failure, inability to biopsy at progression due to poor patient health, etc).

For the aims related to plasma genotyping and serial plasma collection, we may employ a variety of statistical techniques for the analyses of these data. The rate of change at a particular time point may be compared to baseline measures of cfDNA and that measure will be analyzed for association with patient demographics and/or disease characteristics using the Kruskal Wallis test. Landmark analyses of PFS and OS in which the landmark time is defined by the cfDNA measurements at a particular time point, may be used as well. Presence or absence of mutations in plasma will be analyzed for association with other variables using Fisher's exact test. To account for the repeated measures of plasma over time, we may potentially use these data as time varying covariates in multivariable Cox models to study their impact on outcomes like PFS and OS.

If at least 50% of patients (n=10) yield analyzable laboratory results, then this sample size provides 76% power to detect differences in the rate of another binary variable (such as baseline characteristics or abnormality) with frequencies of 5% and 70%, respectively, while testing with a one-sided 0.15-level Fisher's exact test; this also assumes that the underlying prevalence of the genomic marker is 50%, thus splitting the cohort into two groups with 5 patients in each. It is worth noting that the Fisher's test for association between the presence/absence of baseline samples and resistant samples assumes independence between those samples. Given what is known about tumor heterogeneity, the likelihood that the cancer may be altered genomically over time and due to therapy, and the low chance that the same area of a patient's tumor will be biopsied at progression, we believe that independence could be an appropriate assumption. We will, however, explore results via sensitivity analysis using a McNemar's test.

13.1 Study Design/Endpoints

Primary Efficacy Measure:

- Investigate the ORR in patients with tumors exhibiting a *MET* exon 14 mutation.

Secondary Efficacy Measures:

- Evaluate the safety and tolerability of merestinib.
- Determine the OS, PFS, and DoR in patients harboring *MET* mutations.

Exploratory Endpoints:

- Explore the ORR, OS, PFS, and DoR in a small cohort of patients with advanced cancer harboring an *NTRK1, 2,* or *3* rearrangement.
- Investigate the genomic determinants of response and resistance to merestinib by analyzing circulating free tumor DNA for identification of activating mutations in *MET* as well as for detection of resistance mutations.
- Examine the mechanisms of resistance to prior TKIs via a pre-treatment biopsy obtained on patients enrolling to the trial who have received a prior *MET* or *NTRK* inhibitor.
- Assess the genomic determinants of response and resistance to merestinib by analyzing tumor tissue obtained from patients at the time of disease progression.

13.2 Sample Size, Accrual Rate and Study Duration

The planned sample size is 20 patients in the single-arm phase II study of merestinib in patients with *MET* exon 14 mutations. An additional 5 patients will be enrolled into a separate exploratory *NTRK* cohort, for a total of 25 patients.

The planned accrual rate is approximately 3 patients per quarter. Up to an additional year of follow-up will be required on the last participant accrued to observe the patient's response and survival following study therapy, for a total study length of approximately three years. Participants will be identified for enrollment via targeted NextGen Sequencing using the DFCI/BWH OncoPanel or another CLIA-certified method for genotyping.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	1	+	1	=	2
Not Hispanic or Latino	11	+	12	=	23
Ethnic Category: Total of all subjects	12	+	13	=	25
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	0	+	0	=	0
Black or African American	0	+	1	=	1
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	12	+	12	=	24
Racial Category: Total of all subjects	12	+	13	=	25

13.3 Analysis of Primary and Secondary Endpoints

The primary and secondary analyses will include all eligible patients who started assigned therapy. The exception to this includes the planned analysis of toxicity data, which will include all patients who received study drug regardless of eligibility.

13.4 Analysis of Exploratory Endpoints

Analysis for the *NTRK* cohort will include all eligible patients who started assigned therapy.

The results of the NGS obtained on the fresh tissue biopsies and plasma will be compared to the clinical outcomes of the patients. It will help to further identify the genetic characteristics of patients who will respond to treatment with merestinib versus patients who will not, and whether merestinib is able to overcome certain resistance mechanisms in patients who have already received prior *MET* or *NTRK* inhibitors. This data may help with future selection of patient populations appropriate for treatment with *MET* inhibitor therapy.

13.5 Reporting and Exclusions

13.5.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first dose of study medication.

13.5.2 Evaluation of the Primary Efficacy Endpoint

All eligible participants included in the study will be assessed for response, even if there are major protocol therapy deviations. Each participant should be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.